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STUDY DRUG : BRL 29060/PAROXETINE (PAXIL)

**A MULTI-CENTER, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF
PAROXETINE AND IMIPRAMINE IN ADOLESCENTS WITH UNIPOLAR MAJOR
DEPRESSION**

PROTOCOL NUMBER 29060/329

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CONFIDENTIAL

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Principal Investigators:

Name

Study Site Address

SB Medical Monitor

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I, the undersigned, have reviewed the protocol, including Appendices and Amendment #1 and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated.

Investigator's Signature

Date

Month

Year

RYAN002808

STUDY DRUG BRL 29060/PAROXETINE (PAXIL)

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Approved: 26 August 1993

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MAJOR DEPRESSION

Amendment #1 Approved: April 17, 1994

Section 5.2.1 Screening Phase

Revised: 1) Diagnostic assessments will be done using the K-SADS-L in place of the K-SADS-P.
2) In subjects for whom a diagnosis of major depression may be equivocal, the case will be discussed with a principal investigator at a separate site (see Appendix H) who will have access to the interview tapes. If the external reviewer and investigator disagree on inclusion, the external reviewer's opinion shall take precedence.

Rationale: The K-SADS-L is an enhancement of the K-SADS-P in that it includes disorders omitted from the K-SADS-L (e.g. ADHD, antisocial personality disorder, social phobia). Additionally, the K-SADS-L provides for lifetime inquiry. The external review was added to assure uniformity of diagnosis.

Section 5.2.3 Treatment Phase Assessments

Added: In addition to the 12 lead EKG performed at weeks 4 and 8, a rhythm strip EKG will be carried out at all other visits.

Revised: The criterion for heart rate level requiring a dose adjustment has been changed. Patients whose heart rate exceeds 110 bpm on two consecutive visits or 130 bpm at any time will have their dosage decreased by one level if they are at dose level 5 or 6; if the patient is currently treated at dose level 4 or below, the patient will be removed from the study.

Added: Blood levels of imipramine and desipramine will be analyzed in real time following the week 4 and 8 visits. Patients whose combined serum levels of imipramine and desipramine exceed 500 mcg/ml will be withdrawn from the trial.

Rationale: The rhythm strips and the serum analysis have been added to provide additional safety monitoring for patients receiving tricyclic anti-depressants. The revised heart rate criterion agrees with FDA guidelines for studies in adolescents.

Section 7.5.2 Reporting Serious Adverse Events

Revised: The SB medical monitor has been changed from Muriel Young, M.D. to Ivan Gergel, M.D.

SYNOPSIS

- TITLE** A Multi-Center, Double-Blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression
- DRUG UNDER STUDY**
- Imipramine (up to 300 mg)
 - Paroxetine (up to 40 mg)
 - Placebo
- INTENDED INDICATION**
- Treatment of adolescents with unipolar major depression
- OBJECTIVES OF STUDY**
- 1. To compare the safety and efficacy of imipramine and Paroxetine to placebo in the treatment of adolescents with unipolar major depression.
 - 2: To assess the rate of relapse among imipramine, Paroxetine and placebo responders who are maintained on treatment).
- INVESTIGATORS**
- Multicenter, USA
- STUDY DESIGN**
- Multicenter, double blind, placebo controlled, parallel group study
- DURATION OF TREATMENT**
- 8 Week acute phase with a 6 month extension.
- NUMBER OF PATIENTS**
- 300 patients with 100 randomized to each treatment group.

PRINCIPAL END POINTS

- Primary Efficacy Variables

- Change in total HAMD score from beginning of treatment phase to the endpoint of the acute phase.
- The proportion of responders at the end of the eight week acute treatment phase. Responders are defined as 50% or greater reduction in the HAM-D or a HAM-D score equal to or less than 8.

- Secondary Efficacy Variables

- Change from baseline to endpoint (acute phase) in the depression items of the K-SADS-L, global impressions, autonomic function checklist, self perception profile and sickness impact scale.
- The number of patients who relapse during the maintenance phase.

- Safety Variables

- Safety evaluation will be based on adverse experience monitoring, laboratory evaluation, cardiovascular parameters, vital signs and physical examinations.

DURATION OF STUDY

- It is anticipated the study will start in November '93. Recruitment will be for three years, the 8-month study should complete 2Q97.

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1.0 INTRODUCTION

Similarities between adolescent and adult depression in symptomatology, family history, and prospective course provide compelling rationale for investigating the efficacy of antidepressant drug therapy in young patients with depression. But unlike adults, the evidence from trials in adolescents does not support drug efficacy, although the existing studies have collectively evaluated fewer than 200 patients, a number hardly adequate for reliable clinical or statistical inferences.

This apparent difference in response between adults and younger patients has been the subject of much debate, and recent reviews (Conners, 1992; Strober, 1992; Jenson et al., 1992) have focused on three major areas of concern. These include: (1) deficiencies in study design, methodology and conduct; (2) the adequacy of diagnostic criteria and various nosological problems; and (3) developmental issues in that children and adolescents who suffer from adult-like depression may respond in a pharmacologically different manner due to quantitative and/or qualitative developmental differences in neurotransmitter/receptor systems.

The study outlined in this protocol proposes to re-examine antidepressant therapies in adolescents with unipolar major depression using a study plan designed to avoid the perceived flaws of previous studies. This will be a multi-center placebo controlled trial with a target enrollment that will provide sufficient power to detect clinical differences among treatment groups, if these differences exist. The study has rigorous inclusionary and exclusionary criteria so that the study population is more homogenous than reported in previous trials. Diagnostic interviews will be reviewed among the various sites to confirm criteria symptoms of depression and to promote uniformity in diagnosis. Responders will be prospectively defined.

One of the treatment arms will be paroxetine (Paxil), an orally administered antidepressant with a chemical structure unrelated to other selective serotonin reuptake inhibitors (SSRI), or heterocyclic or other antidepressant medications. It has recently been approved by the Food and Drug Administration for the treatment of depression based, in part, on clinical trial data in over 3000 adult patients with major depressive illness. Paroxetine has not been systematically studied in adolescent depression.

A second arm will be imipramine. This tricyclic has been the subject of two small open labeled clinical trials in adolescents, one of which has demonstrated a modest therapeutic response in patients with nondelusional depression.

Please refer to the Paxil (paroxetine) and Tofranil (imipramine) prescribing information for detailed information.

2.0 OBJECTIVES

2.1 Primary

- To compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression .

2.2 Secondary

- To identify predictors of treatment outcomes across clinical subtypes. The following indicators of differential response will be examined, but no directional hypotheses are formulated: endogenous subtype, age at onset, number of prior episodes, duration and severity of current episode, comorbidity with separation anxiety disorder, attention deficit disorder, and conduct disorder.
- To provide information on the safety profile of paroxetine and imipramine when these agents are given for an extended period of time.
- To estimate the rate of relapse among imipramine, paroxetine and placebo responders who are maintained on treatment.

3.0 STUDY PLAN

3.1 Study Design

This will be a multicenter double-blind placebo controlled trial. Adolescents from ages 12 years 0 months through 18 years 11 months inclusive who are currently in an episode of major depressive disorder (DSM-III-R) with a minimum duration of eight weeks and have a Hamilton severity score of 12 or greater will be included in this 8 week double-blind placebo controlled three cell study of the efficacy of paroxetine and the efficacy of imipramine versus placebo.

The treatment period will be of 8 weeks duration. During this time, patients will make weekly visits to the clinic and the effects of treatment on depression will be evaluated using standardized instruments and as well as global assessments. In addition, various safety assessments will be carried out at each visit. Section 5 below describes the study procedures in detail and Appendix D presents the study flow in schematic fashion.

At the completion of the 8 week acute study, clinical responders will be blindly continued on the same medication in a 6 month extension study. Non-responders at the end of the 8 week acute period will be withdrawn and treated openly. Throughout the study, at each site the number of subjects assigned will be approximately equal and each cell will be approximately group balanced for several potentially important covariates.

4.0 STUDY POPULATION

4.1 Number of patients

Three hundred patients will be entered in up to 6 centers and randomized to receive either imipramine (100 patients) paroxetine (100 patients) or placebo (100 patients). Each center will recruit approximately 12 -15 patients per year.

4.2 Inclusion criteria

1. Adolescents between the ages of 12 years 0 month and 18 years 11 months inclusive.

RYAN002817

2. Currently in an episode of major depression (DSM-III-R) for at least 8 weeks. A diagnosis of major depression will be made on summary data aggregating parent and child report. In addition, both adolescent and parent(s) must agree that the adolescent has a disorder meriting treatment.
3. A severity score less than 60 on the Child Global Assessment Scale (C-GAS).
4. A score of 12 or greater on the 17-item Hamilton Depression Scale (HAM-D).
5. Medically healthy as determined by physical examination, medical history and laboratory screening.
6. IQ \geq 80 by Peabody Picture Vocabulary Test.

4.3 Exclusion Criteria

1. Patients with current or lifetime DSM-III-R diagnosis of bipolar disorder, schizo-affective disorder, anorexia nervosa, bulimia, alcohol or drug abuse/dependence, obsessive/compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder.
2. Patients with a current diagnosis (within 12 months) of post traumatic stress disorder (DSM-III-R).
3. Patients who have had an adequate trial of anti-depressants within 6-months prior to beginning this study. An adequate trial is defined as a treatment of at least four weeks or more with imipramine, desipramine, or amitriptyline at a dosage of 150 mg per day or greater, with nortriptyline at a dosage of 50 mg per day or greater, or with fluoxetine at a dosage of 20 mg per day or greater.
4. Patients who have suicidal ideation with a definite plan, or who have made a suicide attempt within the current episode, or who have ever made a suicide attempt by medication overdose.
5. Patients with medical illness which contraindicate the use of heterocyclic antidepressants (e.g. cardiovascular disease).
6. Patients using (1) psychotropic medications including anticonvulsants, anxiolytics, neuroleptics, lithium carbonate, or (2) illicit drugs as documented by a drug screen within two weeks of starting the study.

7. Patients with organic brain disease, epilepsy or mental retardation.
8. Patients who are pregnant or lactating.
9. Sexually active girls who are not using a reliable methods of contraception (oral contraception, surgical sterilization. I.U.D., diaphragm in conjunction with spermicidal foam and condom on partners).
10. Use of an investigational drug within 30 days of entry into the study or within five half lives of the investigation drug (the longer period will apply).

5.0 CONDUCT OF STUDY

The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki (Appendix A) and US 21 CFR Part Protection of Human Subjects, and Part 56 - Institutional Review Board.

5.1 Ethical Considerations

5.1.1 Ethics Review Committee (ERC)/Institutional Review Board (IRB)

This protocol will be submitted to an appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study.

SB will supply relevant data for the investigator to submit to the hospital/university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB's unconditional approval of the protocol and either the written informed consent statement or sample oral witnessed consent form with written information to be given to the subjects will be transmitted to the SB Study Monitor prior to shipment of drug supplies and CRFs to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

The ERC/IRB must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study which are likely to affect the safety of the subjects or the conduct of the study. Approval for such changes must be transmitted in writing to the SB Study Monitor via the investigator.

5.1.2 Informed Consent

The principals of informed consent in the current edition of the Declaration of Helsinki (Appendix A) should be implemented in each clinical study before protocol-specified procedures are carried out.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Information should be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject or the subject's legally authorized representative.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event the signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SB professional and Regulatory Compliance persons.

5.2 Study Method

A patient log will be kept of all patients considered for the study including those not entering the trial. The reasons for excluding patients from the study will be recorded.

The study will consist of three phases: 1) a screening phase of 7-10 days to assess the suitability of a patient for inclusion into the trial; 2) an acute treatment phase of 8 weeks duration in which eligible patients will be randomly assigned to receive either imipramine, paroxetine or placebo, and 3) an extension phase of 6 months duration during which clinical responders will be blindly continued on their randomized medication. Non responders at the end of the 8-week acute period will be withdrawn and treated openly.

Appendix D provides a summary in tabular form of the study procedures and timings.

5.2.1 Screening Phase

Subjects will initially be screened by telephone. All sites will use the Screening for Youth Depression. This screen will review depressive syndrome criteria and major inclusion and exclusion criteria. Subjects who appear likely to meet the study criteria will be evaluated promptly thereafter.

Revised
24 March 1994

Diagnostic assessment will be done using the K-SADS-L with both the adolescent and parent(s). The K-SADS-L semi-structured clinical interview (revised to include present and past psychiatric disorders) will be administered in the fashion described in the instructions for that instrument and will be used to assess the presence or absence of each of the criteria symptoms for depression including a scale for atypical depression. The parent(s) and the adolescent are separately interviewed to assess each symptom. The clinician forms a summary rating based on best overall information combining all sources. For those symptoms where there is significant discrepancy between information provided by the adolescent and information provided by the parent(s), the clinician, adolescent and parent(s) all sit together and discuss the information provided by each source and reach a best conclusion.

Overall global functioning will be assessed at the initial interview using the Child Global Assessment Scale (C-GAS).

All K-SADS interview data will be directly confirmed by a senior clinician (psychiatrist or psychologist) who will interview both the adolescent and parent(s) and will confirm each of the positive criteria for depression by direct interview. The psychiatrist or psychologist will also review each of the items for the Hamilton Depression Rating Scale.

Diagnostic interviews will be audiotaped. If a prospective subject refuses to be audiotaped, this will not be a reason to deny entry. Cases will be reviewed by the Principal investigator or Co-Principal Investigator at the local site who will confirm each patient meets the study entrance criteria.

Added
24 March 1994

If a subject meets 6 or fewer DSM III-R criteria for major depression disorder or the investigator reviewing the diagnosis is uncertain, the investigator must contact one of the principal investigator at a separate site (see Appendix H) to discuss the case. The external reviewer must review the audiotape and return a decision within 2 days. If investigator and external reviewer disagree on inclusion, the external reviewer's opinion shall take precedence.

Following the initial assessment of an adolescent who meets the inclusion criteria and signs the informed consent, the subsequent seven to ten days will be used to obtain medical or psychiatric records of prior treatment where indicated, and to document that the depressive symptomatology is stable after the initial psychiatric contact.

During this time a physical examination will also be conducted to assure the patient is in good medical health. The exam will include clinical laboratory studies (Appendix E) and a cardiovascular evaluation to include 12 lead EKG, heart rate and blood pressure measurements.

At the end of this interval, the adolescent will return to the clinic and will be re-evaluated. Only subjects continuing to meet inclusion criteria (DSM-III-R major depression and the Hamilton Rating Scale total score of 12 or greater) will be included.

Additional instruments to be administered at the end of the assessment period include the Autonomous Functioning Checklist, the Self Perception Profile for Adolescents and the Sickness Impact Scale.

During the assessment interval, a family history will be obtained on all first degree family members using the mother as informant (or other parent or parent surrogate if required). The mother will be interviewed about her lifetime history using the SADS-L and family history of all other first degree relatives using the Family History-Research Diagnostic Criteria (FH-RDC).

A brief description of the various scales and instruments is provided in Appendix F.

5.2.2 Randomization

Randomized Assignment of Subjects to Treatment

A computer generated randomization list will be used in which treatments are balanced within blocks of 6 consecutive patients. Patients will be allocated from 001 to 360. The master randomization list will be held by SmithKline Beecham. The treatment codes may be broken during the study for an individual patient in case of emergency. However, every effort should be made to contact SmithKline Beecham Medical Monitor prior to breaking the treatment code.

5.2.3 Treatment Phase

Assessments during study visits

During the eight week acute phase of the study, each patient will make weekly visits to the clinic. At each visit the following assessments will be carried out:

- HAM-D
- Depression section from the K-SADS-L (every other week)
- Clinical Global Improvement Scale
- Adverse Events
- Cardiovascular Functioning
- Clinical Laboratory Studies (Week 8)

Cardiovascular functioning will be assessed at baseline by obtaining a 12 lead EKG, heart rate, and blood pressure measurements. At each clinic visit, each subject will have a repeat blood pressure sitting and standing and heart rate assessment.

Revised

A 12 Lead EKG will be performed at visits 4 and 8. Rythym strip 24 March 1994 EKG will be carried out at all other visits. Cardiovascular limits to titration (i.e. acceptable limits requiring no change in study medication) will be as follows, using criteria developed by Boris Birmaher, M.D. and James Zuberbuhler, M.D.

resting heart rate < 130*.
resting systolic BP < 140; resting diastolic BP < 85
PR interval < 0.21
QRS interval < 0.12 and less than 150% of baseline
QTC < 0.48

* If the resting heart rate exceeds 110 bpm on two consecutive visits, a dose adjustment is required.

Cardiovascular parameters outside those described above will result in decreasing medication dosage by one tablet level. If a patient is at level 4 or below (see Section 6.0 - Study Drug Administration), he or she will be removed from the study.

Serum Levels

Revised
24 March 1994

Blood samples for analysis of paroxetine as well as imipramine and desipramine will be obtained on all subjects no matter to which treatment they are assigned. Blood will be collected at baseline and after 4 and 8 weeks of treatment and the samples shipped to the Clinical Trials Center of SmithKline Clinical Laboratories (SBCL) in VanNuys California. Written instructions for the collection, preparation and shipping of the samples will be provided to each investigator.

The paroxetine samples will be stored by SBCL until the completion of the study when the plasma will be analyzed for paroxetine concentration. The imipramine/desipramine sample will be analyzed when received by the SBCL. The concentration of imipramine and desipramine data will be retained by SBCL until the completion of the trial. However, if in a given patient, the combined levels of imipramine and desipramine exceed 500 mcg/ml of serum, the investigator will be immediately notified and that patient will be withdrawn from the study. Any further treatment will be as deemed appropriate.

Medical Management -- Psychotherapy

Experience in protocols in depressed adolescents suggest that patients and families expect psychotherapy and are reluctant to consider a course of medication treatment alone, especially where the medication may be solely placebo. On the other hand, a provision of treatment with a psychotherapy which, in retrospect, turned out to be extraordinarily efficacious might well preclude the demonstration of a real, significant, and clinically meaningful medication effect. There are currently several research groups beginning the process of examining different specific psychotherapies (e.g. cognitive behavioral and interpersonal) for adolescent depression. As of yet, however, there are no completed controlled studies which would suggest a "reference" psychotherapy treatment. The present study will include supportive psychotherapy, similar to the management as described by Fawcett in Appendix G. Please note, however, that the procedures in this appendix are meant to serve as a guideline. Where differences exists between the appendix and the protocol (e.g. dosing criteria), the protocol takes precedence.

Modified
24 March 1994

Weekly visits will consist of a 45 minute visit with the therapist. In unusual circumstances, emergency contact of greater duration is permitted. Duration of all contact including phone calls will be systematically documented.

Definition of "responders" and "non-responders" at the end of eight-week acute treatment

To be classified as a "responder" and continue to the continuation phase, a subject must have a HAM-D score ≤ 8 or a decrease in baseline HAM-D total score $\geq 50\%$:

Termination at end of acute study for non-responders

At the end of the acute phase subjects who are "non-responders", as defined above, will be terminated from the study. Medication/placebo will be tapered off over a 7-17 day period at which time their care will be transferred to clinical personnel who are not part of this study. The patient and family, all clinical personnel, and all research personnel will remain blind to medication assignment of all subjects even after termination of the acute phase.

In some subjects, for safety reasons, it may be necessary for the clinical personnel to be informed which medication the subject was on. The decision to unblind the clinical personnel will be made jointly with clinical personnel at the site and clinical personnel at SmithKline Beecham.

5.2.4 Extension study

Subjects who are "responders" at the end of the double-blind acute study will be blindly continued on the current (final) dose of imipramine/paroxetine/placebo for an additional six months. For the purposes of this study, it is estimated that 65% of subjects in both active treatment will be "responders" and 40% of subjects on placebo will be a "responder".

The aims of the continuation phase are: 1) to provide an estimate of the benefits of extended treatment with anti-depressant medications and 2) to provide a safety profile of antidepressants given for an extended period of time.

Procedures for 6-month follow-up:

1. Maintain last medication/placebo dose blindly.
2. Monthly psychiatric and safety assessments:
 - a) Affective section of K-SADS-L interview
 - b) Hamilton depression rating scale
 - c) Adverse Events
 - d) Clinical Global Assessment Scales
 - e) EKG rhythm strip, blood pressure, and heart rate assessment
 - f) Clinical Laboratory Studies (Week 20)
 - g) Serum Drug Levels (Week 20)
3. Assessment at termination of the 6-month extension:
 - a) Full K-SADS-L
 - b) Hamilton Depression rating scale
 - c) Adverse Events
 - d) Clinical Global Assessment Scales
 - e) 12 lead EKG strip, blood pressure, and heart rate assessment
 - f) Clinical Laboratory Studies
 - g) Serum Drug Levels

Revised
24 March 1994

6.0 DRUG SUPPLIES AND PACKAGING

6.1 Formulations

Medication will be administered in the form of green capsules. Paroxetine will be provided as 10 mg over encapsulated tablets, imipramine will be 50 mg over encapsulated tablets while placebo will be provided in a tablet dosage form identical in appearance to paroxetine, over encapsulated.

6.2 Study Drug Administration

Dose of study medication

There will be six dosing levels. All patients will be titrated to level 4 regardless of response. Levels 5 and 6 are optional for those who do not respond after reaching level 4. The timings and dosage at each level are as follows:

	DAY	IMIPRAMINE	PAROXETINE
Level 1	1 - 7	50 mg	20 mg
Level 2	8 - 14	100 mg	20 mg
Level 3	15 - 21	150 mg	20 mg
Level 4	22 - 28	200 mg	20 mg
Level 5	*	250 mg	30 mg
Level 6	*	300 mg	40 mg

6.3 Blinding

The study will use 10 and 20 mg paroxetine tablets and the corresponding placebos. Also to be used will be the 50 mg imipramine tablets and corresponding placebo tablets. The "paroxetine placebos" will be identical in size, color and shape to the 10 and 20 mg paroxetine un-monogrammed tablets. Likewise, the imipramine placebo tablet will be the same size, shape, and color as the active imipramine.

6.4 Concomitant Medication

All concomitant medication taken during the study must be recorded in the case report form with indication, daily dose, and dates of administration.

Subjects will not be allowed to take other psychotropic medications. Subjects will be permitted to take medications without CNS effects for medical illnesses or conditions as necessary. Medications which are not psychotropic, but which may have CNS effects (e.g. prednisone, antihistamines) should be avoided or used for the minimum length of time consistent with good medical care.

6.5 Packaging

The capsules will be packaged using blister cards. One card will hold sufficient supplies for a one week treatment period (10 days). Patients will be instructed to take medication twice daily, one dose in the morning and one at night. The number of capsules for each dose will depend on the dosing level achieved; the minimum number of capsules to be taken daily is two, the maximum is six.

6.6 Labeling and Preparation

For all phases, the tear off portion of the label must be affixed to the CRF when medication is dispensed to the patient. All unused cards must be returned to the sponsor at the end of the study.

6.7 Storage

Study medications must be kept in a locked area and dispensed according to the protocol. Records of dispensed supplies must be kept current on forms which the sponsor will also supply. All unused supplies must be returned to the sponsor at the end of the study.

6.8 Drug Accountability

The investigator will sign that he or she has received the clinical supplies for this study and that the study supplies will be handled and stored safely and properly.

6.9 Assessment of Compliance

A record of the amount of drug dispensed, taken, and returned will be recorded in the CRF for each patient, to assess compliance. The patient will be instructed to return the previous interval's drug container, including any unused medication at each visit.

If a patient takes less than 80% or more than 120% of study drug at each of two consecutive visits, the patient will be considered non-compliant and withdrawn from the study. A patient who misses two consecutive visits will also be withdrawn from the study.

6.10 Overdosage

The following information on overdosage is provided in the prescribing information for Paxil and Tofranil.

For paroxetine, treatment should be consistent with those general measures employed in the management of overdosage with any antidepressant. There are no specific antidotes for paroxetine. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Gastric evacuation either by the induction of emesis or lavage or both should be performed. In most cases, following evacuation, 20 to 30 grams of activated charcoal may be administered every 4-6 hours during the first 24-36 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of paroxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking paroxetine or recently having taken paroxetine who might ingest by accident or intent excessive quantities of a tricyclic antidepressant or a MAO inhibitor. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close observation.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of overdosage.

For imipramine:

Children have been reported to be more sensitive than adults to an acute overdosage of imipramine hydrochloride. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Signs and Symptoms:

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. Blood and urine levels of imipramine may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and are unreliable indicators in the clinical management of the patient. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions.

Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired condition, and signs of congestive failure.

Respiratory depression, cyanosis, and diaphoresis may also be present.

Treatment:

The recommended treatment for overdose with tricyclic antidepressants may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment. Because CNS involvement, respiratory depression and cardiac arrhythmia can occur suddenly, hospitalization and close observation may be necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

In the alert patient, empty the stomach promptly by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Instillation of activated charcoal slurry may help reduce absorption of imipramine.

Minimize external stimulation to reduce the tendency to convulsions. If anticonvulsants are necessary, diazepam, and phenytoin may be useful.

Maintain adequate respiratory exchange. Do not use respiratory stimulants.

Shock should be treated with supportive measures, such as appropriate position, intravenous fluids, and if necessary, a vasopressor agent. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdose with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized

myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised.

Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary.

Hemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis have been generally reported as ineffective because of the rapid fixation of imipramine in tissues. Blood and urine levels of imipramine may not correlate with the degree of intoxication, and are unreliable indicators in the clinical management of the patient.

The slow intravenous administration of physostigmine salicylate has been used as a last resort to reverse CNS anticholinergic manifestations of overdose with tricyclic antidepressants; however, it should not be used routinely, since it may induce seizures and cholinergic crises.

7.0 ADVERSE EXPERIENCES

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below.

7.1 Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation. An adverse experience includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with drug or placebo and whether or not considered drug related.

This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments. Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered an adverse event.

All adverse experiences occurring after the start of the study must be reported. Subject entry into the study is defined as the time at which informed consent is obtained. (This must be before any protocol-specific diagnostic procedures or interventions.) All subsequent adverse experiences, whether no drug (ie. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported **REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.**

At each visit/assessment, adverse experiences will be evaluated by the investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's case record form. The nature of each experience, data and time (where appropriate) of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the case record form.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as 'continuing' should be reviewed. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

Ask the subject a non-leading question such as: "Do you feel different in any way since starting the new treatment/the last assessment."

7.2 Assessment of Severity

Maximum intensity should be assigned to one of the following categories:

Mild: For example, an adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: For example, an adverse experience which is sufficiently discomforting to interfere with normal everyday activities.

Severe: For example, an adverse experience which is incapacitating and prevents normal everyday activities.

7.3 Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: unrelated, probably unrelated, possibly related, related.

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drugs as drugs related, e.g. skin rashes, blood dyscrasia
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

7.4 Following-up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilized. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

7.5 Serious Adverse Experiences

7.5.1 Definition of Serious Adverse Experiences:

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening - definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Disability/incapacitating definition:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

7.5.2 Reporting Serious Adverse Experiences

Any serious adverse experiences which occur during the clinical study or within 30 days (or five half lives whichever is the longer) of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator to the study monitor (by telephone within 24 hours).

All serious adverse experiences must be reported by telephone within 24 hours to the study monitor:

Revised
24 March 1994

The Medical Monitor for this protocol is:

Ivan Gergel, M.D., Director, CNS
Clinical Research, Development and Medical Affairs, North America
SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Ave.
P.O. Box 1510, King of Prussia, PA 19406
Toll Free Number: 1 (800) 877-7074, Ext. 3945
Office: (610) 832-3945
After Hours: 1 (800) 366-8900, Ext. 5900

The Back-up Monitor for this protocol is:

James P. McCafferty, Associate Director
Clinical Research, Development and Medical Affairs, North America
Four Falls Corporate Center
Route 23 and Woodmont Ave.
P.O. Box 1510, King of Prussia, PA 19406
Toll Free Number: 1 (800) 877-7074, Ext. 3431
Office: (610) 832-3431

The telephone report should be followed by a full written summary detailing relevant aspects of the adverse experiences in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality if brought to the attention of the investigator AT ANY TIME after cessation of study medication and linked by the investigator to a previous clinical trial, should be reported to the study monitor.

7.6 Overdosage

Any instance of overdosage (suspected or confirmed) must be communicated to SmithKline Beecham within 24 hours and be fully documented as a serious adverse experience. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

7.7 Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately, unless the protocol states otherwise.

Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 30 days or five half-lives after the treatment period, whichever is longer.

Whenever possible a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

7.8 Breaking the Study Blind

Only in the event of a serious adverse experience which the investigator feels cannot be adequately treated without knowing the identity of the study medication, may the medication code be broken for a particular subject. Every effort must be made to contact an SB Medical Monitor prior to breaking the code. If this is not possible and the situation is an emergency the investigator may break the code and contact the Medical Monitor as soon as possible thereafter.

8.0 SUBJECT COMPLETION AND WITHDRAWAL

8.1 Definitions

For the purpose of this protocol, a patient will be considered to be a "completed subject if they complete the 8 week acute phase". A withdrawal will be any subject who enters the study i.e. gives informed consent, and does not complete the 8 week study period (whether or not subject received study medication).

Because the extension phase is addressing maintenance therapy, it is anticipated that some patients will relapse. Accordingly, the definition of a "completed subject will be modified to be any patient who completes the full six months of therapy or any patient who withdrawals from therapy because of a relapse".

8.2 Procedures for Handling Withdrawals

It is anticipated that in a few subjects the study will be terminated early because of medication side effects. potential reasons for early termination include cardiovascular side effects beyond those permitted (see above), allergic reaction to medications, etc. Decisions for early study termination for medical or other reasons should be the responsibility of the principal investigator at each site. In all cases, subjects terminated early for any reason including medical reasons will be included in data analysis. Decision to terminate or not will be made blind to actual medication/placebo status--the blind will be broken only after termination is decided.

Should a patient decide to terminate the study early, a discontinuation taper is strongly recommended. If this accepted by the family, the medication will be tapered off in a linear fashion over a 7 to 17 day period.

8.3 Reason for withdrawal

A patient may withdraw from the study prior to completion for one of six possible reasons:

1. Adverse experiences including intercurrent illness
2. Insufficient therapeutic effect
3. Deviation from protocol including non-compliance
4. Lost to follow-up
5. Termination by SB
6. Other (specify).

The investigator should determine the primary reason for withdrawal and cite the one reason.

9.0 DATA EVALUATION

9.1 Criteria for Efficacy

9.1.1 Primary efficacy variables

- a) The change in total HAMD score from beginning of the treatment phase to the endpoint of the acute phase.
- b) The proportion of responders at the end of the eight week acute treatment phase.

9.1.2 Secondary efficacy variables

- a) Changes from baseline to endpoint in the following parameters:
 - Depression items in K-SAD-L
 - Global Impressions
 - Autonomic Function Checklist
 - Self Perception Profile
 - Sickness Impact Scale.
- b) Predictors of response (endogenous subtypes, age, prior episodes, duration and severity of present episode, comorbidity with separate anxiety, attention deficit, and conduct disorder).
- c) The number of patients who relapse during the maintenance phase.

9.2 Statistical Methods

9.2.1 Comparisons of interest

The comparison of primary interest is active treatment versus placebo. Hypotheses concerning these comparison will be tested at the alpha level of 0.05

9.2.2 Sample size determination

This study is designed to have adequate power to detect a clinically meaningful difference in both active-placebo comparisons at a two tailed alpha level of 0.05 and power 0.80. The sample size estimates are further based on an effect size of 0.40. The rationale for this effect size is as follows:

- A difference of 4 in the HAMD Total change from baseline scores at endpoint. This is a smaller difference than that seen in previous studies with antidepressants in adults, yet it is large enough to be clinically meaningful, and
- A standard deviation of 10. This is 20% larger than observed in studies with anti-depressants in adults and should reflect the greater variability in response expected in adolescent depression.

These parameter estimates result in 100 patients per treatment group.

9.3 Efficacy Analysis

9.3.1 Intent to Treat Analysis

All patients who receive double-blind medication will be considered as part of the ITT population. This patient population will be considered the primary population.

9.3.2 Patients Valid For The Efficacy Analysis

All patients randomized to study treatment and for whom at least one valid post-treatment efficacy evaluation is available will be valid for inclusion in an 'intent-to-treat' analysis. Patients who meet the following criteria will be eligible for the efficacy analysis:

- a) No major protocol violation exists with regard to inclusion or exclusion criteria.
- b) No other major protocol violation during the first 8 weeks of active treatment has occurred.

Only primary efficacy variables will be analyzed using this population. Patients to be excluded from the efficacy analysis will be identified before the randomization code is broken.

9.3.3 Statistical Methodology

Psychometric scales using at least an ordinal measurement scale will be analyzed using parametric analysis of variance, effects in the model will include treatment, investigator and treatment by investigator interaction. If the treatment by investigator interaction is not significant ($p > 0.1$) the interaction term will be dropped from the model. This analysis will be performed using the General Linear Models procedure of the SAS system. The ordinal scales which have very few levels (such as the CGI Severity of Illness) will also be analyzed using nonparametric methodology to ensure that the results are consistent across modes of analysis.

Dichotomous variables such as response (based on HAMD criteria) will be analyzed using Logistic Regression methodology. Effects in the model will include treatment, investigator, and treatment by investigator interaction; if the interaction is not significant then it will be dropped from the model. These analyses will be performed using the LOGISTIC procedure of the SAS system.

Summary statistics will be presented for demography, disease history, and baseline measures of efficacy.

An analysis of covariance will be performed to evaluate the effect of possibly important prognostic variables on the HAMD total score at endpoint. These include endogenous subtype, age at onset, gender, number of prior episodes, duration and severity of current episode, comorbidity with separate anxiety disorder, attention deficit disorder and conduct disorder.

9.3.4 Test of Significance

Tests of hypothesis regarding model assumptions such as the significance of treatment by investigator interactions will be made at the 10% level.

All other statistical tests will be two-tailed and performed at the 5% significance level.

9.3.5 Patient Characteristics At Baseline

Demographic and diagnostic variables at baseline will be checked for homogeneity between the treatment groups. If major differences exist for variables predictive of treatment response, their impact on the trial results will be investigated.

9.4 Safety Analysis

9.4.1 Patients Valid for Clinical Safety & Tolerability

All patients who receive coded medication will be assessed for clinical safety and tolerability.

9.4.2 Adverse Experiences

Adverse experiences will be coded for each subject with reference to body system and preferred terms. The treatment groups will be compared regarding the incidence of the reported adverse experiences with reference to both preferred term and body system. The comparison between treatments with regard to incidence of adverse experiences will be performed primarily by using descriptive statistics.

9.4.3 Other Clinical Safety Variables

Information regarding demographic data, vital signs, physical examination, adverse experiences and abnormal laboratory values will be presented as listings and tables. All deviations from the study protocol and study withdrawals will be documented.

10.0 ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice, important administrative obligations relating to investigator responsibilities, monitoring, archiving data, confidentiality and publications must be fulfilled as given in Appendix B.

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APPENDIX ADECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in
biomedical research involving human subjects

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964,
Amended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975,
35th World Medical Assembly,
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.